and found the steady-state assumption applicable, it would seem that tetralin would behave the same in our system as does cumene, providing the aforementioned conditions are met.

Acknowledgment.—It is a pleasure to acknowledge many stimulating and helpful discussions with Dr. Glen A. Russell.

Experimental

Materials.—Cumene (Phillips 99 mole per cent. minimum) was rectified in a large Podbielniak column (750 plates) and the center fraction collected; b.p. 69–70° at 41 mm., n^{20}_{D} 1.4910. This fraction was chromatographically filtered through activated silica gel or alumina and stored under nitrogen at 0°. Acetic acid was refluxed with chromium trioxide for 12–15 hours and then distilled through a Vigreux column, the center fraction being collected. The water content of this fraction was determined by Karl Fischer titration following which the theoretical quantity of acetic anhydride was added and the whole heated to reflux for 48 hours. Following this treatment the water content as determined by Karl Fischer titration was 1 mg./ml. At this point the theoretical quantity of boron triacetate necessary to react with the residual water was added and the whole heated to reflux for 16 hours. Finally, the acid was distilled under nitrogen through a Vigreux column and the center fraction collected and stored under nitrogen. Vapor phase chromatography indicated that the acid was pure. Azodiisobutyronitrile (Eastman Kodak Co.) was recrystallized several times from methanal; m.p. 102° dec. 2,6-Di-*t*-butyl-4-methylphenal (Koppers, "food-grade") was purified by 10 successive recrystallizations from *n*-hexane carried out as follows; the phenol was dissolved in *n*-hexane at room temperature following which the solution was cooled with rapid stirring to −60°. This treatment was repeated successively until the mother liquors showed no evidence of color. The final product (m.p. 69.5–70°) was stored under nitrogen at 0°. Commercial cobaltous acetate tetrahydrate was purified by several recrystallizations from 50% aqueous acetic acid. The resulting product was dehydrated by pumping at 80° and 1 mm. for approximately 60 hours. The emission spectrum of the salt showed trace amounts of copper, chromium and manganese to be present. Standard solutions of the anhydrous salt were prepared in anhydrous acetic acid. In every case these solutions analyzed satisfactorily for cobaltous ions and were shown by Karl Fisher titration to contain less than 0.01% water. The solutions were stored under nitrogen until used.

Oxidation Procedure.—The initiator was added to the oxidation flask as a 0.1 M solution in benzene. The benzene was removed by evacuating at 15–20 mm. for approximately two hours. The reagents (cumene, acetic acid, standard cobaltous acetate solution, DBPC) appropriate to the run were added by pipet and the oxidation flask, which consisted of a heavy-walled erlenmeyer flask, attached to a reciprocating rack contained in a thermostated oil-bath and the rate of oxygen absorption measured by manual control of the mercury level in the gas buret.

Analytical Procedures. Hydroperoxides.—The yields of hydroperoxide were determined by the stannous chloride procedure of Barnard and Hargrave[17] and carried out as described previously.[4] Blank determinations showed that cobaltous ions had no effect on the procedure.

Isolation of Acetophenone.—Acetophenone was isolated and identified as its DNP derivative, m.p. 248–249°, mixed m.p. 249°; reported[18] 250°. Due to the acetic acid solvent it was not possible to analyze quantitatively for the acetophenone, as had been done in the autoxidations employing chlorobenzene as solvent. However, it was demonstrated conclusively that the acetophenone did not arise by reaction between cumene hydroperoxide and DNP. It was found that these two reagents reacted very slowly under the conditions of the experiments, whereas the addition of DNP reagent to the oxidant gave an almost instantaneous reaction yielding the DNP derivative of acetophenone. In view of the yields of hydroperoxide and considering the earlier results in chlorobenzene solution, the most reasonable conclusion is that acetophenone is a primary oxidation product in the acetic acid system also.

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[17] D. Barnard and K. R. Hargrave, *Anal. Chem. Acta*, **5**, 476 (1951).

[18] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948.

SCHENECTADY, N. Y.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

1,2,3,4,7,7-Hexachloro-2-norbornene Derivatives

BY WAYLAND E. NOLAND AND LOWELL R. SMITH

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Diels–Alder reactions of hexachlorocyclopentadiene led to the formation of the adducts I from nitroethylene, VI after hydrolysis of the adduct from itaconic anhydride, and X from dimethyl acetylenedicarboxylate. The nitro adduct I was converted to a sodium salt II which yielded the chloro (IVa) and bromo (IVb) derivatives on halogenation. The failure of II to undergo the Nef or related solvolysis reactions is attributed in part to an inductive effect of the chlorine substituents, since the corresponding acid III was shown to be 63 times as strong as the unchlorinated acid. Chemical reduction of I yielded the corresponding amine V. The diacid VI yielded, besides the anhydride VII, a monomethyl ester (VIII) and, under conditions which overcame the much greater steric hindrance of the second carboxyl, the dimethyl ester IX. Saponification of X yielded the diacid XI, which has properties different from a diacid described in the literature to which the same structure previously had been assigned.

The failure of salts of the 5-nitro-2-norbornenes to undergo the Nef reaction, and the novel rearrangement which occurs instead with 5-nitro-2-norbornene,[1] led us to examine the behavior under similar conditions of the partially chlorinated derivative, 1,2,3,4,7,7-hexachloro-*endo*-5-nitro-2-norbornene (I). This derivative was synthesized in 61% yield by the Diels–Alder reaction of hexachlorocyclopentadiene with nitroethylene. In contrast to the more extensive Diels–Alder reactions of cyclopentadiene with nitroölefins,[2] the steric limits of the Diels–Alder reaction of hexachlorocyclopentadiene appear to have been reached in the simplest case, with nitroethylene itself; 2-nitropropene, 1-nitropropene and β-nitrostyrene do not appear to react with refluxing hexachlorocyclopentadiene, and excellent recoveries of hexachlorocyclopentadiene were obtained.

The adduct I forms a sodium salt (II), which was isolated as a hydrate. With this sodium salt all attempts to produce a Nef reaction or a rear-

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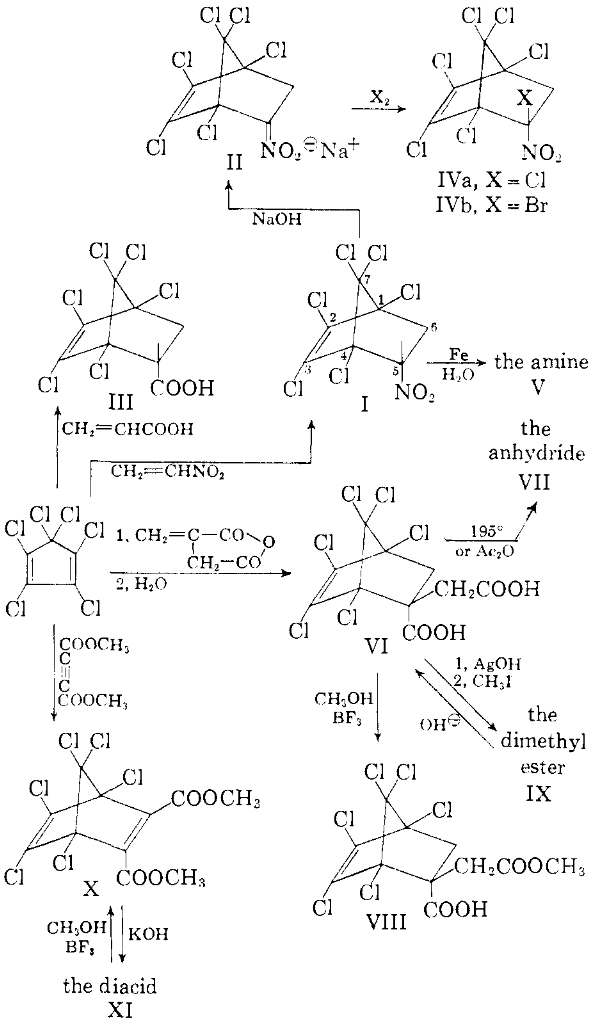
[1] W. E. Noland, J. H. Cooley and P. A. McVeigh, THIS JOURNAL, **81**, 1209 (1959).

[2] (a) W. E. Noland and R. E. Bambury, *ibid.*, **77**, 6386 (1955); (b) W. E. Noland, R. E. Counsell and M. H. Fischer, *J. Org. Chem.*, **21**, 911 (1956).

rangement analogous to that occurring with the unchlorinated derivative, 5-nitro-2-norbornene,[1] were unsuccessful. Addition of a dioxane–water slurry of the sodium salt II to a solution of aqueous 20% sulfuric acid and dioxane at 0°, 55 or 100° gave regenerated nitro compound I in yields of 82, 93 and 96%, respectively. The failure here of the Nef reaction, as well as the related solvolysis reaction accompanied by rearrangement, could be attributed in part to steric hindrance by chlorine preventing solvolysis at C_2 or C_5 in the *aci* form of 1,2,3,4,7,7-hexachloro-*endo*-5-nitro-2-norbornene (I). It seems certain, however, that inductive electron removal by chlorine plays an important part, perhaps by withdrawing electrons in the *aci* form away from the nitro group and toward C_5, at which solvolysis might have occurred, thus reducing the polarity of the C–N bond. A similar failure of the Nef reaction due to the inductive effect has been reported with γ-perfluoro nitroalcohols and nitroalkanes, such as 1,1,1-trifluoro-3-nitro-2-propanol and 1,1,1,2,2,3,3-heptafluoro-5-nitropentane.[3]



In order to provide a quantitative measure of the relative inductive effects operative at C_5 in 5-nitronorbornene and in its hexachloro derivative I, we have determined the acidities of the corresponding 5-norbornene-*endo*-2-carboxylic acids. The pK_a of 5-norbornene-*endo*-2-carboxylic acid[4] is 6.35 in 50% (by volume) aqueous ethanol at 31°. 1,4,5,6,7,7-Hexachloro-5-norbornene-*endo*-2-carboxylic acid (III), which has been described previously only in the patent literature,[5] was obtained in 67% yield from the Diels–Alder reaction of hexachlorocyclopentadiene with acrylic acid. Its pK_a is 4.55 in 50% aqueous ethanol at 27 and 31°; thus, the chlorinated acid is 63 times as strong an acid as its unchlorinated derivative—good evidence for an important electron-withdrawing inductive effect in the chlorinated acid III as well as in the related nitro compound I.

In contrast to the case with the nitro adduct I, which can be dissolved in liquid bromine and recovered unchanged in high yield, the sodium salt is readily chlorinated or brominated in 98% yields to the corresponding 5-chloro (IVa) or 5-bromo (IVb) derivatives. In these 5-halo derivatives the halogen entering the 5-position is assigned the *exo* configuration on the grounds that *exo* approach by halogen would be the least sterically hindered.

Hydrogenation of the nitro adduct I was attempted at 2 atm. over a 10% palladium-on-charcoal catalyst. No uptake of hydrogen occurred in ethyl acetate, acetic anhydride or 2:1 (by volume) dioxane–acetic anhydride solutions. In ethanol or acetic acid solutions about 2 moles of hydrogen was consumed, but acetylation of the oily products gave no crystalline amide derivative. Chemical reduction with iron powder, water and ammonium chloride catalyst gave the oily amine, 1,4,5,6,7,7-hexachloro-5-norbornene-*endo*-2-amine (V) in 7% yield, which was characterized through its acetyl, phenylurea and hydrochloride derivatives.

The Diels–Alder reaction of hexachlorocyclopentadiene with itaconic anhydride, followed by hydrolysis of the adduct, gave the corresponding diacid, formulated as *endo*-2-carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic acid (VI), in 71% yield. This diacid thermally dehydrates readily, or can be converted by conventional anhydride exchange with acetic anhydride, to the corresponding anhydride VII, which has been described in the patent literature.[6] Esterification of the diacid with methanol and sulfuric acid as catalyst gave no bicarbonate-insoluble product (the diester) but only a monomethyl ester (VIII, bicarbonate-soluble). Similarly, only the monoester VIII was obtained in 60% yield from the reaction with methanol catalyzed by boron fluoride etherate. Addition of methanol to a cooled, but previously refluxed solution of the monoester in thionyl chloride resulted only in 79% recovery of the monoester. The sterically hindered carboxyl

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(3) D. J. Cook, O. R. Pierce and E. T. McBee, THIS JOURNAL, **76**, 83 (1954).

(4) We are indebted to Professor William E. Parham for providing us with a sample of this acid, prepared according to the procedure of O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

(5) S. B. Soloway, J. G. Morales and J. Van Overbeek (to Shell Development Co.), U. S. Patent 2,758,918, August 14, 1956 [*C. A.*, **50**, 17307 (1956)].

(6) P. Robitschek and C. T. Bean, Jr., *Ind. Eng. Chem.*, **46**, 1628 (1954); (to Hooker Chemical Corp.), U. S. Patent 2,752,361, June 26, 1956 [*C. A.*, **51**, 1276 (1957)].

group of the diacid was successfully esterified through the reaction of the disilver salt with excess methyl iodide, giving the dimethyl ester IX in 59% yield. Alkaline saponification of the diester regenerated the diacid in 82% yield.

The Diels–Alder reaction of hexachlorocyclopentadiene with dimethyl acetylenedicarboxylate gave the corresponding adduct, dimethyl 1,4,5,6,7,-7-hexachloro-2,5-norbornadiene-2,3-dicarboxylate (X), in 72% yield. All attempts to hydrolyze this dimethyl ester in acid media gave back only unchanged ester, but alkaline saponification gave the corresponding diacid XI, m.p. 192.5–193.5°, in 78% yield. This diacid has pK_{a_1} of 3.75 and pK_{a_2} of 6.15 in 50% (by volume) aqueous ethanol at 32°. Re-esterification of the diacid gave back the original dimethyl ester X, indicating that no rearrangement was likely to have occurred during the formation of the diacid. The diacid did not form an anhydride under the usual conditions for anhydride exchange. When a sample of the diacid was dissolved in acetic anhydride and the acetic anhydride evaporated at steam-bath temperature under reduced pressure, only the original diacid was recovered unchanged, with no evidence of anhydride formation. Irradiation of an ether solution (25 cc.) of the diacid (3.0 g.) for 10 hours with ultraviolet light from a lamp resulted only in recovery of unchanged starting material in 90% yield. Under similar conditions the unchlorinated diacid of the same structure has been shown to photoisomerize to quadricyclo[2,2,1,0,^{2,6}0^{3,5}]heptane-2,3-dicarboxylic acid.[7]

The reaction of hexachlorocyclopentadiene and acetylenedicarboxylic acid in refluxing benzene has been reported to give a diacid XI, m.p. 162–163°, in 45% yield.[8] The melting point of this diacid is 30° lower than ours; we are unable to account for the difference. In our hands the procedure described[9] for synthesis of the diacid left, upon evaporation of the benzene, much unreacted hexachlorocyclopentadiene and a relatively small amount of an immiscible brown oil which could not be crystallized. Other attempts to bring about the reaction using refluxing anisole, toluene or dioxane as solvent media gave no crystalline product; in the latter case 83% of the acetylenedicarboxylic acid was recovered unchanged.

Several other potential dienophiles failed to react with hexachlorocyclopentadiene. Ethoxyacetylene, methyleneaminoacetonitrile and methyl isopropenyl ketone appear not to react with hexachlorocyclopentadiene in refluxing solution, as considerable amounts of unreacted diene were recovered and no crystalline products were isolated. Similarly, hexachlorocyclopentadiene and tetracyanoethylene did not react in refluxing toluene solution, and good recovery of tetracyanoethylene was achieved. Hexachlorocyclopentadiene and fumaric acid did not react in refluxing dioxane solution, and the full amount of fumaric acid was recovered unchanged.

The compounds described in this work are being tested for insecticidal activity by Professor Laurence K. Cutkomp of the Department of Entomology and Economic Zoology, University of Minnesota, St. Paul Campus. The results will be reported elsewhere.

Experimental

Melting points were determined on a calibrated Kofler micro hot-stage.

1,2,3,4,7,7-Hexachloro-*endo*-5-nitro-2-norbornene (I).—Ice-cold nitroethylene[10] (60.0 g. 0.821 mole) was added to ice-cold hexachlorocyclopentadiene (814 g., 2.98 moles). The mixture was warmed very slowly to 100° and then heating was stopped. The temperature dropped to 85° and remained there for 0.5 hour before dropping again. After the golden brown reaction mixture had been set aside for 48 hours it was warmed to 100° for 0.5 hour and then to 120° for one hour. A small amount of immiscible brown oil was discarded and unreacted hexachlorocyclopentadiene was distilled off at 70–80° (5 mm.). The tarry residue was dissolved in methanol and the methanol evaporated, leaving a slushy gel. This gel was evacuated in a vacuum desiccator warmed with a heat lamp for 5 hours. The resulting solid was slurried with aqueous 30% ethanol and filtered for 24 hours through a vacuum filter equipped with a rubber dam. The resulting solid was dissolved in methanol, treated with charcoal, and water added to the filtered solution, causing precipitation of an amorphous solid (135 g.). Slow evaporation of the filtrate gave a second crop which, after treatment with charcoal and reprecipitation from methanol-water, gave 37 g. more of solid, making a total of 172 g. (0.499 mole, 61%) of pure product. The soft, sticky white solid can be further purified, if desired, by crystallization from slowly evaporating aqueous 90% methanol or better by sublimation at 130° (5 mm.). The amorphous solid or sublimate yields small crystals on long standing. The soft, sticky white crystals of 1,2,3,4,7,-7-hexachloro-*endo*-5-nitro-2-norbornene sublime at 159–160° to a clear film which becomes fluid at 170–174°. They have a camphor-like odor; $\nu_{C=C}$ 1604; ν_{NO_2} 1564, 1359 cm.$^{-1}$ in CCl_4.

Anal. Calcd. for $C_7H_3NO_2Cl_6$ (345.84): C, 24.31; H, 0.87; N, 4.06. Found: C, 24.31; H, 0.88; N, 3.94.

Sodio-1,2,3,4,7,7-hexachloro-5-nitro-2-norbornene (II).—1,2,3,4,7,7-Hexachloro-*endo*-5-nitro-2-norbornene (4.94 g., 0.0143 mole) was dissolved in methanol (5 cc.) and aqueous 20% sodium hydroxide (20 cc.) was added, causing a precipitate to form. The mixture was shaken until all of the precipitate had redissolved. The solution was then chilled in an ice-bath for 0.5 hour and the resulting precipitate (5.76 g., 0.00989 mole, 69%) was filtered off. Acidification of the filtrate regenerated starting material (0.63 g., 13%).

Recrystallization of the precipitated salt from 90% ethanol yielded sodio-1,2,3,4,7,7-hexachloro-5-nitro-2-norbornene dodecahydrate as white crystals, which darkened gradually upon heating but did not melt below 250°; the crystals charred without explosion.

Anal. Calcd. for $C_7H_2NO_2Cl_6Na \cdot 12H_2O$ (584.02): wt. loss after drying at 78° *in vacuo*, 37.02. Found: wt. loss, 37.65. Calcd. for $C_7H_2NO_2Cl_6Na$ (367.83): C, 22.86; H, 0.55; N, 3.81. Found (after drying): C, 21.94; H, 0.88; N, 3.75.

1,2,3,4,*exo*-5,7,7-Heptachloro-*endo*-5-nitro-2-norbornene (IVa).—1,2,3,4,7,7-Hexachloro-*endo*-5-nitro-2-norbornene (10.0 g., 0.0289 mole) was dissolved in a solution of sodium hydroxide (1.3 g., 0.032 mole) in water (150 cc.), resulting in immediate precipitation of the sodium salt. Chlorine was passed into the mixture until solid no longer precipitated. The white precipitate was filtered off, washed with water, and recrystallized from methanol–water, yielding 1,2,3,4,-*exo*-5,7,7-heptachloro-*endo*-5-nitro-2-norbornene as white needles (10.8 g., 0.0284 mole, 98%), m.p. 213–215° in a sealed capillary; $\nu_{C=C}$ 1601 in CCl_4, 1596 in Nujol; ν_{NO_2} 1577, 1330 in CCl_4, 1563, 1331 cm.$^{-1}$ in Nujol.

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(7) S. J. Cristol and R. L. Snell, THIS JOURNAL, **80**, 1950 (1958).

(8) E. T. McBee, J. D. Idol, Jr., and C. W. Roberts, *ibid.*, **77**, 6674 (1955).

(9) James D. Idol, Jr., Ph.D. Thesis, Purdue University, Lafayette, Ind., August, 1955.

(10) (a) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947); (b) W. E. Noland, H. I. Freeman and M. S. Baker, THIS JOURNAL, **78**, 188 (1956).

Anal. Calcd. for $C_7H_2NO_2Cl_7$ (380.29): C, 22.11; H, 0.53; N, 3.68. Found: C, 21.97; H, 0.61; N, 3.50.

***exo*-5-Bromo-1,2,3,4,7,7-hexachloro-*endo*-5-nitro-2-norbornene (IVb).**—A suspension of sodio-1,2,3,4,7,7-hexachloro-5-nitro-2-norbornene dodecahydrate (18.5 g., 0.0318 mole) in water (200 cc.) was shaken with excess bromine. The resulting white precipitate was filtered off and recrystallized from methylene chloride–methanol, yielding *exo*-5-bromo-1,2,3,4,7,7-hexachloro-*endo*-5-nitro-2-norbornene as white crystals (13.2 g., 0.0312 mole, 98%), m.p. 190–194°; $\nu_{C=C}$ 1600 in CCl_4, 1593 in Nujol; 1575, 1330 in CCl_4, 1559, 1333 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_7H_2NO_2BrCl_6$ (424.75): C, 19.79; H, 0.48; N, 3.30. Found: C, 19.86; H, 0.58; N, 3.33.

1,4,5,6,7,7-Hexachloro-5-norbornene-*endo*-2-amine (V) Derivatives.—1,2,3,4,7,7-Hexachloro-*endo*-5-nitro-2-norbornene (24.0 g., 0.0695 mole) was dissolved in a solution prepared from 1 *N* aqueous ammonium chloride[11] (24 cc.) and ethanol (150 c.c). Iron powder (24 g., 0.43 g. atom) was added and the mixture stirred for 3 hours at room temperature and then set aside for 24 hours. Most of the ethanol was removed under reduced pressure and the residue was extracted with benzene (100 cc.). The benzene layer was extracted with 15% hydrochloric acid (2 × 50 cc.). The acid extracts were basified with dilute sodium hydroxide solution and the basic solution was extracted with benzene (100 cc.). Evaporation of the benzene under reduced pressure left a small amount of residual oil (1.5 g., 0.0048 mole, 7%). This oil was characterized through the following derivatives:

Acetyl derivative: from methylene chloride–light petroleum (b.p. 60–68°), white crystals, m.p. 188°; ν_{NH} 3240, 1555; $\nu_{C=O}$ 1657; $\nu_{C=C}$ 1601 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_7NOCl_6$ (357.90): C, 30.20; H, 1.97; N, 3.91. Found: C, 30.34; H, 2.10; N, 4.20.

Phenylurea derivative: from methanol–water, white crystals, m.p. 243–244° dec.; ν_{NH} 3370, 3300, 1561; $\nu_{C=O}$ 1652; $\nu_{C=C}$ 1597 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{10}N_2OCl_6$ (434.98): C, 38.35; H, 2.32; N, 6.44. Found: C, 38.54; H, 2.37; N, 6.51.

Hydrochloride: by sublimation at 155° (2 mm.), white crystals, dec. 170–180°; ν_{NH} 3410, 2020, 1528; $\nu_{C=C}$ 1598 cm.$^{-1}$ in KBr disk.

Anal. Calcd. for $C_7H_6NCl_7$ (352.32): C, 23.86; H, 1.72; N, 3.98. Found: C, 23.84; H, 1.78; N, 3.99.

1,4,5,6,7,7-Hexachloro-5-norbornene-*endo*-2-carboxylic Acid (III).—A solution of acrylic acid (28 g., 0.39 mole) in hexachlorocyclopentadiene (139 g., 0.49 mole) was warmed to 100°, but without further external heating the temperature rose rapidly to 160°. The exothermic reaction was cooled rapidly to 80° and, after the reaction had subsided, was set aside at room temperature for 24 hours. The resulting solid was dissolved in methylene chloride, the solution concentrated, and light petroleum (b.p. 60–68°) added, causing precipitation of 1,4,5,6,7,7-hexachloro-5-norbornene *endo*-2-carboxylic acid as white crystals (90 g., 0.26 mole, 67%), m.p. 182–183°, reported[5] m.p. 181–182.5°. The analytical sample was further purified by sublimation. The pK_A is 4.55 in 50% (by volume) aqueous ethanol at 27° and 31°.

Anal. Calcd. for $C_8H_4O_2Cl_6$ (344.85): C, 27.86; H, 1.17. Found: C, 27.95; H, 1.47.

Amide derivative: from aqueous 70% methanol, white crystals, m.p. 162–163°, reported[5] m.p. 161–162°.

***endo*-2-Carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic Acid (VI).**—A solution of itaconic anhydride (33.6 g., 0.300 mole) and hexachlorocyclopentadiene (164.0 g., 0.601 mole) in toluene (50 cc.) was refluxed at 120° for 4 hours. Unreacted hexachlorocyclopentadiene was removed by steam distillation. The residual oil was extracted with ether and the ether solution was dried over calcium chloride and decolorized with charcoal. Light petroleum (b.p. 40–75°) was added, causing precipitation of *endo*-2-carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic acid as white crystals (86.0 g., 0.213 mole, 71%), m.p. 189–190°. The infrared spectrum contains broad carboxyl hydroxyl absorption and $\nu_{C=O}$ 1712, 1698 (doublet); $\nu_{C=C}$ 1602 cm.$^{-1}$ in Nujol. The delicate balance between adequate drying of the analytical sample and thermal dehydration to the anhydride usually leads to high carbon and hydrogen values.

Anal. Calcd. for $C_{10}H_6O_4Cl_6$ (402.89): C, 29.81; H, 1.50. Found: C, 30.46; H, 1.72.

***endo*-2-Carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-acetic Acid Cyclic Anhydride (VII). A. By Thermal Dehydration.**—*endo*-2-Carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic acid (5.0 g., 0.0124 mole) was heated at 195° in an oil-bath for 5 minutes, during which time water distilled. The residue was dissolved in methylene chloride and decolorized with charcoal. The addition of light petroleum (b.p. 40–75°) caused precipitation of *endo*-2-carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic acid cyclic anhydride as white crystals (3.8 g., 0.0099 mole, 80%), m.p. 134–135°, reported[6] m.p. 131–134.6°.

B. By Anhydride Exchange with Acetic Anhydride.—The diacid (10.0 g., 0.0248 mole) was added to acetic anhydride (50 cc., 0.56 mole) and the mixture was warmed until solution occurred. The acetic acid and anhydride were then evaporated under reduced pressure and the brownish residue was dissolved in methylene chloride. The solution was decolorized with charcoal and then light petroleum (b.p. 40–75°) was added, causing the anhydride to precipitate as white crystals (8.2 g., 0.0212 mole, 86%), m.p. 134–135°, reported[6] m.p. 131–134.6°; $\nu_{C=O}$ 1855, 1775; $\nu_{C=C}$ 1615 cm.$^{-1}$ in a KBr disk.

Anal. Calcd. for $C_{10}H_4O_3Cl_6$ (384.88): C, 31.20; H, 1.05. Found: C, 30.95; H, 1.17.

Methyl *endo*-2-Carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetate (VIII).—A solution of *endo*-2-carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic acid (10.0 g., 0.0248 mole) and boron fluoride etherate (Baker and Adamson technical grade, 5 cc.) in methanol (50 cc.) and methylene chloride (70 cc.) was refluxed for 10 hours. The methanol and methylene chloride were removed under reduced pressure and the oily residue solidified upon standing. Recrystallization from methylene chloride–light petroleum (b.p. 40–75°) yielded methyl *endo*-2-carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetate as white crystals (6.2 g., 0.0149 mole, 60%), m.p. 156–157°; ν_{OH} 3230; $\nu_{C=O}$ 1748, 1697; $\nu_{C=C}$ 1603 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_8O_4Cl_6$ (416.92): C, 31.69; H, 1.93. Found: C, 31.72; H, 1.97.

The product was soluble in aqueous 10% sodium bicarbonate.

Methyl 1,4,5,6,7,7-Hexachloro-*endo*-2-methoxycarbonyl-5-norbornene-*exo*-2-acetate (IX).—Aqueous 10% silver nitrate was added to a solution of *endo*-2-carboxy-1,4,5,6,7,7-hexachloro-5-norbornene-*exo*-2-acetic acid (8.03 g., 0.020 mole) in aqueous sodium bicarbonate (6.7%, 50 cc.) until precipitation was complete. The precipitated silver salt was filtered off and washed with water, methanol, and ether and then dried for an hour. The aqueous filtrate gave a white precipitate upon addition of sodium chloride solution, indicating that excess silver nitrate had been present. Excess methyl iodide (57 g., 0.40 mole) was added to the dried silver salt, causing almost immediate separation of yellow silver iodide as the methyl iodide began to reflux. When spontaneous refluxing of the methyl iodide ceased, external heat was applied and the mixture was refluxed for one hour. Ether (25 cc.) was added to the cooled mixture and the silver iodide was filtered off on a sintered glass funnel. The ethereal filtrate was washed with aqueous 10% sodium bicarbonate (25 cc.), dried over calcium chloride, and filtered through a charcoal pad. The ether and unreacted methyl iodide were distilled off and the residue was dried at 100° (7 mm.) for 2 hours, leaving an oil (5.1 g., 0.0118 mole, 59%), $n^{28.8}_D$ 1.5273. Distillation yielded the analytical sample of methyl 1,4,5,6,7,7-hexachloro-*endo*-2-methoxycarbonyl-5-norbornene-*exo*-2-acetate as a colorless, very viscous oil, b.p. ~ 125° (0.8 mm.), $n^{27.8}_D$ 1.5289, $\nu_{C=O}$ 1733; $\nu_{C=C}$ 1602 cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{12}H_{10}O_4Cl_6$ (430.95): C, 33.44; H, 2.34. Found: C, 33.30; H, 2.64.

Dimethyl 1,4,5,6,7,7-Hexachloro-2,5-norbornadiene-2,3-dicarboxylate (X). A. By the Diels–Alder Reaction.[12]—A

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[11] (a) V. O. Lukashevich and M. A. Voroshilova, *Compt. rend. acad. sci. U.R.S.S.*, **2**, 394 (1935); *Org. Chem. Ind.* (*U.S.S.R.*), **4**, 253 (1937) [*C. A.*, **32**, 2091 (1938)]; Russian Patent 51,050, May 31, 1937 [*C. A.*, **33**, 4601 (1939)]; (b) W. E. Noland, B.A. thesis, University of Wisconsin, 1948; (c) S. M. McElvain, "The Characterization of Organic Compounds," rev. ed., The Macmillan Co., New York, N. Y., 1951, pp. 144–145.

[12] This compound was first prepared by John A. Melin in this Laboratory.

solution of dimethyl acetylenedicarboxylate (77.1 g., 0.543 mole) in hexachlorocyclopentadiene (292.1 g., 1.07 mole) was heated to 140°, but without further external heating the temperature rose rapidly to 230° while the light yellow solution became deep carmine red. The exothermic reaction was cooled rapidly to 0°. The solution was then reheated at 147° for 2 hours and finally briefly at 200°. The solution was steam distilled until unreacted hexachlorocyclopentadiene no longer came over in the distillate. The residual aqueous mixture was extracted with ether and the ether extract was treated with charcoal and dried over calcium chloride. The dried ether solution was concentrated by evaporation and methanol was added, causing precipitation of dimethyl 1,4,5,6,7,7-hexachloro-2,5-norbornadiene-2,3-dicarboxylate as white crystals (162.1 g., 0.391 mole, 72%), m.p. 85–86°. The near ultraviolet spectrum in 95% ethanol contained no maxima and only ill-defined inflections at about 288 mμ (log ϵ 2.42) and 230 (3.58), with rising end absorption (at 220 mμ log ϵ is 3.80 and at 215, 4.00); $\nu_{C=C}$ ~ 1720 in $CHCl_3$, 1725 in Nujol; $\nu_{C=O}$ 1629, 1596 cm.$^{-1}$ in $CHCl_3$ and in Nujol.

Anal. Calcd. for $C_{10}H_6O_4Cl_6$ (414.90): C, 31.84; H, 1.46. Found: C, 32.06; H, 1.57.

B. By **Re-esterification of the Diacid.**—A solution of 1,4,5,6,7,7-hexachloro-2,5-norbornadiene-2,3-dicarboxylic acid (2.0 g., 0.0052 mole) and boron fluoride etherate (Baker and Adamson technical grade, 5 cc.) in methanol (50 cc.) was refluxed for 5 hours. Sodium bicarbonate solution (5%, 30 cc.) caused the diester to precipitate. Recrystallization from aqueous 80% methanol gave white crystals (1.2 g., 0.0029 mole, 56%), which gave no depression in mixed melting point with the sample from Part A. The infrared spectra of the two samples in Nujol were identical.

1,4,5,6,7,7-Hexachloro-2,5-norbornadiene-2,3-dicarboxylic Acid (XI).[12]—A mixture of dimethyl 1,4,5,6,7,7-hexachloro-2,5-norbornadiene-2,3-dicarboxylate (25.0 g., 0.0603 mole) and aqueous 5% potassium hydroxide (200 cc.) was refluxed for 6 hours. The resulting dark brown solution was cooled to room temperature, filtered to remove traces of unreacted starting material, and then cooled to 0°. Concentrated sulfuric acid was added slowly, with vigorous shaking, to *p*H 2, causing precipitation of a white solid, assumed to be the monopotassium salt since on ignition it left a residue which gave an orange flame test. Additional concentrated sulfuric acid (20 cc.) was added and the mixture was stirred for 5 minutes. The resulting solid precipitate no longer left a residue upon ignition. The mixture was extracted with ether, which dissolved the precipitate. The ether extract was dried over calcium chloride and treated with charcoal. Most of the ether was evaporated off, light petroleum (b.p. 40–75°) was added, and the solution was set aside overnight. The resulting precipitate was recrystallized from a fairly large amount of water, yielding the hydrate as white crystals (25.5 g.), which dehydrate at ~120–150°, m.p. 190–191.5°. The hydrate shows a great tendency to oil out of concentrated water solutions and invariably oils out of mixtures of water with acetone, methanol, ethanol or dioxane. Ether–light petroleum (b.p. 40–75°) may be used as a recrystallization solvent, but this combination does not produce as pure a product as does water.

Drying of the hydrate at 100° (1 mm.) for 5 hours yielded 1,4,5,6,7,7-hexachloro-2,5-norbornadiene-2,3-dicarboxylic acid as white crystals (18.2 g., 0.0470 mole, 78%) m.p. 192.5–193.5°, reported[8] m.p. 162–163°; ν_{OH} ~2690, 2550; $\nu_{C=O}$ 1715, 1694; $\nu_{C=C}$ 1637, 1606 cm.$^{-1}$ in Nujol; pK_{a1} is 3.75 and pK_{a2} is 6.15 in 50% (by volume) aqueous ethanol at 32°.

Anal. Calcd. for $C_9H_2O_4Cl_6$ (386.85): C, 27.94; H, 0.52. Found: C, 27.97; H, 0.72.

MINNEAPOLIS 14, MINN.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXVII. Synthesis of Alkylating Agents Derived from 6-Amino-6-deoxy-D-glucose

BY ELMER J. REIST, ROLAND R. SPENCER AND B. R. BAKER

RECEIVED AUGUST 14, 1959

The synthesis of 6-[bis-(2-chloroethyl)-amino]-6-deoxy-D-glucose hydrochloride (XXIII), 6-[(2-chloroethyl)-ethylamino]-6-deoxy-D-glucose hydrochloride (XXIV) and 6-(2-chloroethylamino)-6-deoxy-D-glucose hydrochloride (XXV) *via* the key intermediate 3,5-O-benzylidene-1,2-O-isopropylidene-6-O-*p*-tolylsulfonyl-D-glucofuranose (XI) is described.

A rationale for the design of specific irreversible enzyme inhibitors was presented in paper XVII of this series.[2] This rationale proposed that substrates, properly substituted by an alkylating group, could fit the specific enzyme site for the substrate, then replace a nearby active hydrogen by alkylation, thus resulting in specific irreversible inactivation of the enzyme.

Recent work devoted to the synthesis of nitrogen mustards in which the carrier is a metabolite, or resembles a metabolite, has resulted in several promising anticancer compounds, such as phenylalanine mustard (sarcolysin),[3] *m*-phenylalanine mustard,[2,4] chlorambucil,[5] uracil mustard,[6] and benzimidazole mustard.[7] As part of the rationale,[2] it was proposed that a nitrogen mustard, attached to a substrate as a carrier, might be a type of compound that could operate as a specific irreversible enzyme inhibitor. If such is the case, then a "one-armed" mustard should be as good as, or possibly even better than, the corresponding "two-armed" mustard as an anticancer agent.

Vargha and co-workers[8,9] have synthesized several nitrogen mustards in the sugar series which have some interesting biological activities. N,N-Bis-(2-chloroethyl)-D-glucosamine hydrochloride (I)

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[1] This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, P. A. Hart and B. R. Baker, *J. Org. Chem.*, **24**, 1640 (1959).

[2] H. F. Gram, C. W. Mosher and B. R. Baker, THIS JOURNAL, **81**, 3103 (1959).

[3] F. Bergel, V. C. E. Burnop and J. A. Stock, *J. Chem. Soc.*, 1223 (1955); L. F. Larinov, A. S. Khokhlov, E. N. Shkodinskaia, O. S. Vasina, V. I. Trusheikina and M. A. Novikova, *Lancet*, **269**, 169 (1955).

[4] T. S. Osdene, D. N. Ward, W. H. Chapman and H. Rakoff, THIS JOURNAL, **81**, 3100 (1959).

[5] J. L. Everett, J. J. Roberts and W. C. J. Ross, *J. Chem. Soc.*, 2386 (1953).

[6] D. A. Lyttle and H. G. Petering, THIS JOURNAL, **80**, 6459 (1958).

[7] E. Hirschberg, A. Gellhorn and W. S. Gump, *Cancer Research*, **17**, 904 (1957).

[8] L. Vargha, L. Toldy, Ö. Fehér and S. Lendvai, *J. Chem. Soc.*, 805 (1959).

[9] L. Vargha, Ö. Fehér and S. Lendvai, *ibid.*, 810 (1959).